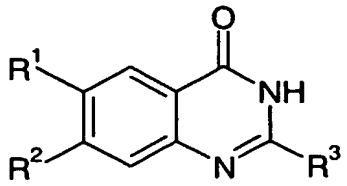
Quinazolinone Derivatives Useful As Anti-hyperalgesic Agents

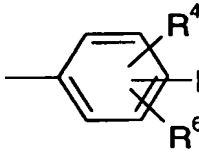
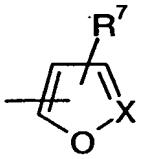
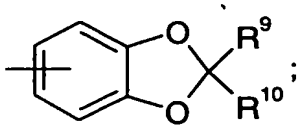
The present invention relates to novel quinazolinone derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

More particularly the present invention provides, in a first aspect, a quinazolinone of formula I



(I)

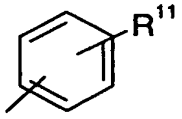
wherein

R^1 is hal;  ;  or  ;

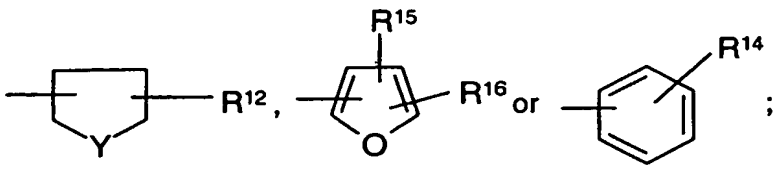
X is N or CR^8;

R^2 is hal; nitro; C_1-C_6alkylcarbonyl; C_1-C_6alkyl or C_3-C_6cycloalkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; amino; C_1-C_6alkyl-amino, di(C_1-C_6alkyl)-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or mono-, di- or trisubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; (C_1-C_6alkyl)$_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  or

-O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1, 2, 3, 4, 5 or 6;

R^5 and R^6, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{11} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{12} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{13} is H or C_1-C_6alkyl;

R^{14} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl; and

R^{15} and R^{16}, independently, are H; hal; or C_1-C_6alkyl;

in free base or acid addition salt form.

Terms used in this specification have the following meanings:

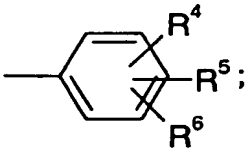
"C_1-C_6alkyl" denotes straight chain or branched C_1 to C_6-alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl.

"C_1-C_6alkoxy" denotes straight chain or branched C_1 to C_6-alkyl-oxy, e.g. methoxy, ethoxy, n-propoxy or isopropoxy.

"Hal" denotes halogen which may be I, Br, Cl or F.

Compounds of the invention exist in free or salt, e.g. acid addition salt form. The invention is to be understood as including the compounds of formula I in free as well as in salt form, e.g. as trifluoroacetate or hydrochloride salt. Suitable pharmaceutically acceptable acid addition salts for pharmaceutical use in accordance with the invention include in particular the hydrochloride salt.

In formula I the following significances are preferred independently, collectively or in any combination or sub-combination:

(a) R^1 is 

;

(b) R^2 is isopropyl;

(c) R^3 is methyl or amino; more preferably methyl;

(d) R^4 is in meta position as defined above; or more preferably R^4 is in meta position and is C_1-C_4alkoxy or C_3-C_4cycloalkylC_1-C_4alkoxy;

(e) R^5 is in para position and is hal; more preferably Cl;

(f) R^6 is H or halogen; more preferably H;

(g) R^7 or R^8 is H or methyl; more preferably methyl;

(h) R^{14} is C_1-C_4alkoxy; more preferably methoxy;

(i) R^{12} is methyl;

(k) R^{13} is methyl;

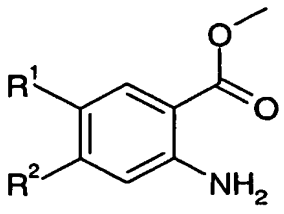
(l) n is 0 or 1 or 2; and

(m) R^9 and R^{10} are hydrogen or fluoro.

In addition to the foregoing the present invention also provides a process for the production of a compound of formula I which process comprises coupling suitable starting compounds applying methods known to the skilled artisan.

More particularly the invention provides a process for the production of a compound of formula I comprising the steps of:

a) for the production of a compound of formula I wherein R^3 is not NH_2, reacting a compound of formula II



(II)

wherein

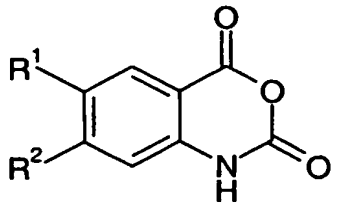
R^1 and R^2 are as defined in formula I,

with a compound of formula III

$$N\equiv C-R^3 \qquad \text{(III)}$$

wherein R^3 is as defined in formula I in the presence of an acid, e.g. hydrogen chloride; or

b) for the production of a compound of formula I wherein R^3 is NH_2, reacting a compound of formula IV



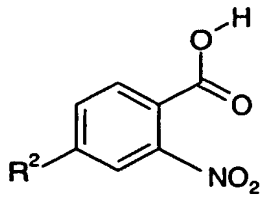
(IV)

wherein R^1 and R^2 are as defined in formula I,
with 2-ethyl-2-thiopseudourea hydrobromide;
and recovering the obtained compound in free or in salt form, e.g. acid addition salt form.

Compounds of formula I resulting from the above process may be further derivatised, e.g. as described in Example 1, i.e. for the conversion of 6-(4-chloro-3-fluoro-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one into 6-(4-chloro-3-cyclopropylmethoxy-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one.

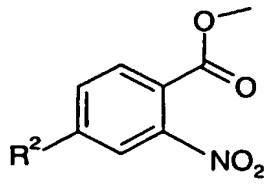
Compounds of formula III are known or may be prepared from corresponding known compounds, e.g. as described in Examples 1 or 2. Compounds of formula IV are known or may be prepared from corresponding known compounds, e.g. as described in Example 59.

Compounds of formula II are new and constitute part of the present invention. They may be prepared from corresponding known starting materials according to the general knowledge of a person skilled in the art, e.g. as described in Examples 1 and 2. For instance, an acid of formula V

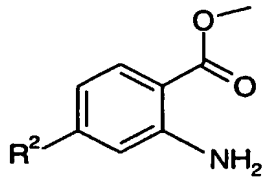


(V),

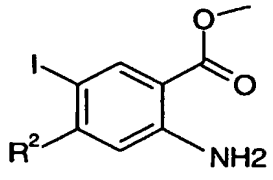
wherein R^2 has the meaning as provided above for a compound of formula I, is transformed into an ester in a manner known as such to provide a nitro compound of formula VI


(VI),

wherein R^2 has the meaning as provided above for a compound of formula I. The nitro compound of formula VI is then reduced to the corresponding amine of formula VII

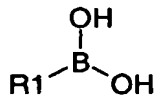

(VII),

wherein R^2 has the meaning as provided above for a compound of formula I, e.g. by reaction with hydrogen in the presence of a suitable catalyst, such as palladium on activated carbon. The obtained amine of formula VII can be further reacted to the iodide of formula VIII,


(VIII),

wherein R^2 has the meaning as provided above for a compound of formula I, e.g. by reaction firstly with silver (I) sulfate and secondly with iodide in a suitable solvent.

The obtained iodide of formula VIII can be reacted with the boronic acid of formula IX


(IX)

wherein R^1 has the meaning as provided above for a compound of formula I, providing a compound of formula II.

Working up the reaction mixtures according to the above processes and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice-versa.

Compounds of formula I in optically pure form can be obtained from the corresponding racemates according to well-known procedures, e.g. HPLC with chiral matrix. Alternatively, optically pure starting materials can be used.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known *per se* by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned below. The protecting groups are then wholly or partly removed according to one of the methods described there.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products.The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove and hereinafter.

The protection of such functional groups by protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of organic chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag, Stuttgart 1974.

All process steps described here can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably such as are inert to the reagents used and able to dissolve these, in the absence or presence of catalysts, condensing agents or neutralising agents, for example ion exchangers, typically cation exchangers, for example in the H^+ form, depending on the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from -100°C to about 190°C, preferably from about -80°C to about 150°C, for example at -80 to -60°C, at room temperature, at - 20 to 40°C or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under argon or nitrogen.

The compounds of formula I and their pharmaceutically acceptable acid addition salts (hereinafter: the agents of the invention) have beneficial pharmacological activity and are useful as pharmaceuticals. In particular the agent of the invention exhibit human vanilloid antagonistic activity. More particularly, the agents of the invention, e.g. the compounds of examples 1 - 60 are active, e.g. at the human vanilloid receptor type 1 (VR1).

Vanilloid receptor interaction of the agents of invention is demonstrated by the following test 1.

Test I: Fluorescence assay

Cultures of Chinese Hamster Ovary (CHO) cells expressing human VR1 ion channels are prepared according to standard protocols [McIntyre et al., British Journal of Pharmacology 132: 1084-1094 (2001)]. The activity of test compounds are investigated using a fluorescence assay utilising calcium sensitive dyes to measure changes in intracellular calcium ion concentration . The cells are plated at a density of 40,000 per well on 96 well Costar black, clear bottomed plates cultured at 37°C in 5% CO_2 in MEM medium overnight. On the day of the assay, cells are incubated in 2μM fura-2/AM (Molecular Probes) made up in assay buffer [Hank's Balanced Salt Solution (HBSS, Invitrogen) containing 10mM N-2-(hydroxyethylpiperazine-N'-[2-ethanesulfonic acid) (HEPES), pH 7.4] containing 0.01% pluronic F-127 for 40min at room temperature. After washing twice with assay buffer, 100μl assay buffer, or test compounds (range from 1nM to 10 μM final) where appropriate, are added to each well and the plate incubated for ten minutes at room temperature and then placed in a Molecular Devices Flexstation. The fluorescence is measured over 1min at 4s intervals using excitation wavelengths of 340 and 380nm and emission of 520nm. Human vanilloid receptor 1 ion channels are stimulated by application of either the agonist capsaicin or low pH. At approximately 17s, 20μl of capsaicin made up at 6 fold the required final concentration were transferred to the cells. For pH experiments, 100μl HBSS alone pH 7.4 (containing test compounds) is added to the cells and 20μl of 60mM 2-[N-morpholino]ethane sulfonic acid (MES) in HBSS transferred to the cells. The pH of this solution is adjusted such that it gives the desired pH when diluted 1:6. The ratio of fluorescence intensities following excitation at 340 and 380nm is calculated for each time point. The agonist-evoked response is calculated as the mean of the ratios in the four time-points following stimulation minus the basal ratio.

In the above test the agents of the invention effectively block Ca-uptake in the range from about 1nM to about 10 μM, especially 25 to 100 nM, especially 50 or 60 nM.

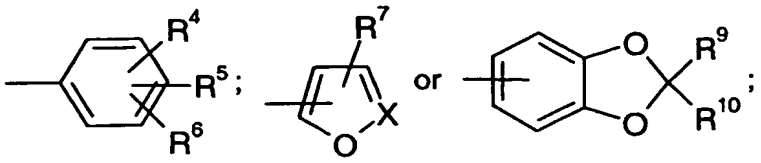
In view of the above, the agent of the invention are useful in the prevention and treatment of diseases and conditions in which human VR1 activation plays a role or is implicated. Such conditions include in particular chronic pain, i.e. for the treatment of hyperalgesia and, in particular, for the treatment of severe chronic pain; neuropathic pain associated with post-herpetic neuralgia, amputations ("phantom limb pain"), reflex sympathetic dystrophy and other chronic nerve injuries; inflammatory pain, e.g. chronic inflammatory pain, bone and

joint pain (osteoarthritis), cancer pain, myofascial pain (muscular injury, fibromyalgia) and perioperative pain (general surgery, e.g. associated with burns, sprains, fracture or the like, subsequent to surgical intervention, gynecologic surgery); or in asthma, for example, aluminosis, anthracosis, inflammatory diseases for example inflammatory airways disease, e.g. Chronic Obstructive Pulmonary Disease; asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis, and rhinitis; smooth muscle relaxants, e.g. for the treatment of spasm of the gastro-intestinal tract or uterus, e.g. in the therapy of Crohn's disease, ulcerative colitis or pancreatitis, inflammatory bowel disease, cystitis, e.g. interstitial cystitis, pancreatitis, and uveitis; inflammatory skin disorders and rheumatoid arthritis, inflammatory skin disorders, for example psoriasis and eczema.

Activity specifically as analgesic agents may be demonstrated in accordance with standard test methods, e.g. as described in the following test 2.

Test 2: Anti-hyperalgesic effects in a model of neuropathic pain in the rat
Peripheral neuropathy is induced by partial ligation of the left sciatic nerve. Mechanical hyperalgesia is assessed from paw withdrawal thresholds measured on the ipsilateral (ligated) and contralateral (non-ligated) hindpaws using standard paw pressure methods. Drug effects are studied 11-15 days post ligation. The mean paw withdrawal threshold ± s.e.m. for the left (ligated) paw is compared to that of the right (non-ligated) paw. Pharmaceutical Compound is administered, e.g. orally in 20 % cremophor/water in a volume of 1 ml. The post-drug percentage hyperalgesia values are obtained by comparison to the pre-drug value for the right (non-ligated) paw; this enables a true measure of the reduction in hyperalgesia to be obtained without the added complication of any drug effects on the right paw. Single oral administration of Pharmaceutical Compound produces a highly effective reversal of mechanical hyperalgesia in the partially denervated rat hind paw. Pharmaceutical Compounds produce a reversal of mechanical hyperalgesia at 30 mg/kg and show a rapid onset of activity with a long duration of action. Thus, Pharmaceutical Compounds are potent and efficacious anti-hyperalgesic agents following oral administration in a rat model of neuropathic pain.

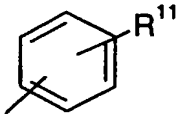
Preferred are quinazolinones of formula I wherein

R^1 is hal;  ;

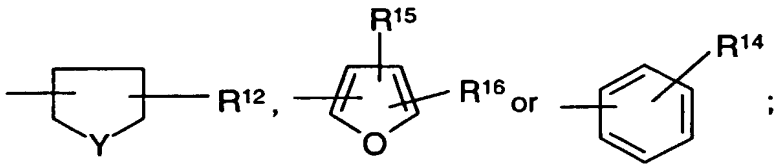
X is N or CR^8;

R^2 is C_1-C_6alkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; amino; C_1-C_6alkyl-amino, di(C_1-C_6alkyl)-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or mono-, di- or trisubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; (C_1-C_6alkyl)$_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  or

-O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1, 2, 3, 4, 5 or 6;

R^5 and R^6, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{11} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

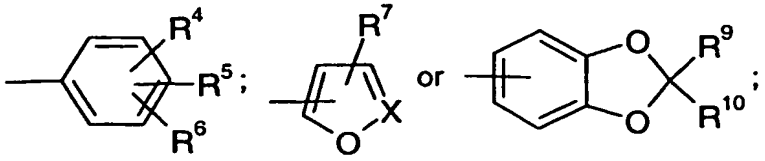
R^{12} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{13} is H or C_1-C_6alkyl;

R^{14} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl; and

R^{15} and R^{16}, independently, are H; hal; or C_1-C_6alkyl.

Very preferred are those quinazolinones of formula I wherein

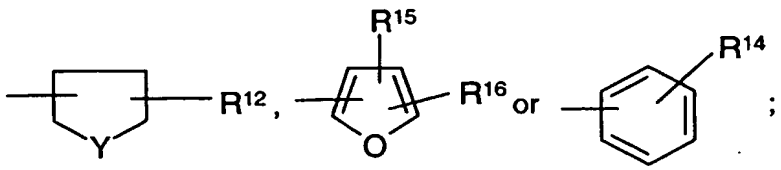
R^1 is hal; 

X is N or CR^8;

R^2 is C_1-C_6alkyl;

R^3 is C_1-C_6alkyl or amino;

R^4 is hal; hydroxy; amino; C_1-C_6alkyl-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or monosubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; $(C_1$-C_6alkyl$)_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy, or -O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1 or 2;

R^5 and R^6, independently, are H; hal; or C_1-C_6alkoxy;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

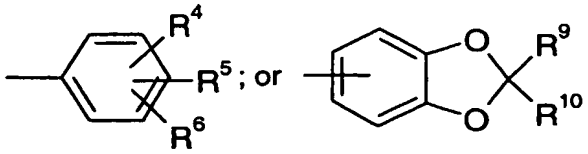
R^{12} is H;

R^{13} is C_1-C_6alkyl;

R^{14} is H; or C_1-C_6alkoxy; and

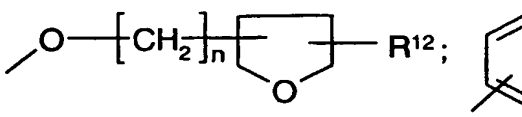
R^{15} and R^{16} are H.

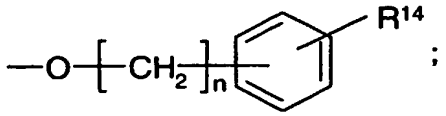
Even more preferred are quinazolinones of formula I wherein

R^1 is hal; 

R^2 is hal; nitro; C_1-C_6alkylcarbonyl; C_1-C_6alkyl or C_3-C_6cycloalkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; C_1-C_6alkyl; C_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; halogenoC_1-C_6alkoxy; C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; $(C_1$-C_6alkyl$)_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  ;  ; or

 ;

wherein n is 0, 1, 2, 3, 4, 5 or 6;

R^5, R^6, R^{11} and R^{14}, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{12} is H or C_1-C_6alkyl; and

R^9 and R^{10}, independently, are H or hal;

in free base or acid addition salt form.

Most preferred are those compounds disclosed in the Examples below.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.05 to about 150, preferably from about 0.1 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 0.5 to about 5000, preferably from about 1 to about 500mg of an agent of the invention, conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agents of the invention can be administered in vivo either alone or in combination with other pharmaceutical agents, e.g. agents effective in the treatment of diseases and conditions in which the human VR1 activation plays a role or is implicated including cyclooxygenase-2 (COX-2) inhibitors, such as specific COX-2 inhibitors (e.g. celecoxib, COX189, and rofecoxib) or in general nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. acetylsalicylic acid, propionic acid derivatives), tricyclic antidepressants (e.g. Anafranil®,

Asendin®, Aventyl®, Elavil®, Endep®, Norfranil®, Norpramin®, Pamelor®, Sinequan®, Surmontil®, Tipramine®, Tofranil®, Vivactil®, Tofranil-PM®), anticonvulsants (e.g. gabapentin), $GABA_B$ agonists (e.g. L-baclofen), opioids and CB receptor agonists, e.g. CB_1 receptor agonists.

The pharmaceutical compositions for separate administration of the combination partners and for the administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners, according to the invention can be prepared in a manner known per se and are thus suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application.

Pharmaceutical compositions contain, for example, from about 0.1 % to about 99.9 %, preferably from about 20 % to about 60 %, of the active ingredients. Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of a combination partner contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any condition mentioned above.

In still a further aspect the present invention provides a method for the treatment of any condition mentioned above, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention.

Abbreviations

conc.	concentrated
DCM	dichloromethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
HPLC	high pressure liquid chromatography
Me	methyl
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
THF	tetrahydrofuran

Example 1: Preparation of 6-(4-Chloro-3-cyclopropylmethoxy-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one

a) Preparation of 4-Isopropyl-2-nitro-benzoic acid: A stirred solution of 2-nitro-4-cymene (8g, 0.0446mol) in t-butoxy bis(dimethylamino)methane (10g, 0.0574mol) is heated at 110°C for 10h. The deep red solution is cooled to room temperature and the excess reagent and by-products are removed under reduced pressure. The residue is dissolved in tert. butanol (600ml) and a solution of potassium acetate (51.35g, 0.372mol) in water (150ml) is added. Potassium permanganate (51.35g, 0.325mol) is added portion-wise to this mixture producing a slight exotherm. After 3h, the mixture is filtered through celite and the celite pad washed with water (500ml) and methanol (1000ml). The volatiles are evaporated under reduced pressure and the residue partitioned between ethyl acetate and water. The aqueous layer is acidified to pH3 using hydrochloric acid and the mixture is extracted with ethyl acetate (3x 150ml). The combined ethyl acetate extracts are washed with saturated brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 4-Isopropyl-2-nitro-benzoic acid as a brown solid. This is sufficiently pure for use in the next step without further purification. ^1H NMR ($CDCl_3$, 400MHz) δH (ppm) 10.0 (1H, br s), 7.82 (1H, d, J = 8.0Hz), 7.64 (1H, d, J = 1.5Hz), 7.50 (1H, dd, J = 1.5, 8.0Hz), 3.05 (1H, m), 1.30 (6H, d, J = 6.9Hz).

b) Preparation of 4-Isopropyl-2-nitro-benzoic acid methyl ester: To a stirred solution of 4-isopropyl-2-nitro-benzoic acid (6.7g, 0.032mol) in dry DMF (100ml) at room temperature is

added cesium carbonate (16.0g, 0.049mol). After 30 minutes, iodomethane (6.84g, 0.048mol) is added and the mixture is stirred at room temperature for 16h. The mixture is poured into water (500ml) and extracted with ethyl acetate (3x100ml). The combined EtOAc extracts are washed with water (200ml), saturated brine (100ml), dried ($MgSO_4$), filtered and evaporated to give a red oil. Purification by column chromatography on silica gel using cyclohexane/ethyl acetate (10:1) as eluant gave 4-isopropyl-2-nitro-benzoic acid methyl ester

c) Preparation of 2-Amino-4-isopropyl-benzoic acid methyl ester: To a stirred solution of 4-isopropyl-2-nitro-benzoic acid methyl ester (6.0g, 0.027mol) in methanol (200ml) at room temperature under argon is added 10% palladium on activated carbon (5.4g). The suspension is evacuated and purged with hydrogen three times and then stirred at room temperature for 18h. The reaction is then placed under argon atmosphere and filtered through a pad of celite. The celite pad is washed with ethyl acetate and the filtrate and washings evaporated under reduced pressure to give a colourless oil. Purification by column chromatography on silica gel using cyclohexane/ethyl acetate (10:1) as eluant gave 2-amino-4-isopropyl-benzoic acid methyl ester.

d) Preparation of 2-Amino-5-iodo-4-isopropyl-benzoic acid methyl ester: To a stirred solution of 2-amino-4-isopropyl-benzoic acid methyl ester (4.73g, 0.0245mol) in ethanol (100ml) at room temperature is added silver (I) sulfate (7.64g, 0.0245mol). A solution of iodine (6.23g, 0.0245mol) in ethanol (200ml) is added via a pressure-equalised dropping funnel at room temperature and the mixture is then stirred at room temperature for 1h. After filtration of the crude reaction mixture through a pad of celite, the ethanol is evaporated and the residue partitioned between water/ethyl acetate and extracted with ethyl acetate (3 x 100ml). The ethyl acetate extracts are combined and washed with saturated brine, dried ($MgSO_4$), filtered and evaporated to give a red solid. The crude product could be used directly or purified by chromatography on silica gel using cyclohexane/ethyl acetate (10:1) as eluant followed by recrystallisation from hexanes to give 2-Amino-5-iodo-4-isopropyl-benzoic acid methyl ester. ^1H NMR ($CDCl_3$, 400MHz) δH (ppm) 8.25 (1H, s), 6.55 (1H, s), 5.69 (2H, br s), 3.85 (3H, s), 3.06 (1H, m), 1.19 (6H, d, J = 6.8Hz).

e) Preparation of 4-Chloro-3-fluorobenzeneboronic acid: A stirred solution of 4-bromo-1-chloro-2-fluorobenzene (25g, 0.119mol) and triisopropylborate (30.5ml, 0.131mol) in dry THF (500ml) under argon is cooled to -100°C and n-butyllithium (52.5ml of a 2.5M solution in

hexanes, 0.131mol) is added dropwise over 15min. The reaction mixture is allowed to warm gradually to room temperature over 18h before it is quenched by the addition of 2M hydrochloric acid (250ml) and stirred at room temperature overnight. The THF is removed under reduced pressure, the aqueous residue is diluted with water (500ml) and the mixture is extracted with diethyl ether (3 x 200ml). The combined ether extracts are washed with saturated brine (200ml), dried ($MgSO_4$), filtered, evaporated and dried *in vacuo* to give a colourless solid - a mixture of 4-Chloro-3-fluorobenzeneboronic acid and the functionally equivalent cyclotriboroxane.

f) Preparation of 4-Amino-4'-chloro-3'-fluoro-6-isopropyl-biphenyl-3-carboxylic acid methyl ester: To a stirred mixture of 4-chloro-3-fluorobenzeneboronic acid (12.3g, 0.071mol), 2-amino-5-iodo-4-isopropyl-benzoic acid methyl ester (18g, 0.0564mol) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) (1.35g, 1.65mmol) in dry DMF (250ml) under argon is added sodium carbonate (140ml of a 2M aqueous solution, 0.28mol). The mixture is heated at 80°C for 16h, cooled to room temperature and poured into diethyl ether (500ml). The ether layer is separated, washed with water (3 x 250ml) and then saturated brine (50ml), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a brown oil. Purification by column chromatography on silica gel using cyclohexane and then cyclohexane/ethyl acetate (50:1) as eluant gave pure product. The impure product-containing fractions are combined, evaporated and recrystallised from n-hexane with a trace of ethyl acetate to give further 4-Amino-4'-chloro-3'-fluoro-6-isopropyl-biphenyl-3-carboxylic acid methyl ester.

g) Preparation of 6-(4-Chloro-3-fluoro-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one: Hydrogen chloride gas is bubbled through a solution of 4-amino-4'-chloro-3'-fluoro-6-isopropyl-biphenyl-3-carboxylic acid methyl ester (12.6g, 0.039mol) in dry acetonitrile (250ml) for 15min at room temperature. The bubbling is then stopped and the mixture heated at reflux for 2h, cooled to room temperature and the volatiles removed under reduced pressure. The colourless residue is poured into water (500ml) and sodium bicarbonate is added portion-wise until no further CO_2 evolution takes place. The mixture is extracted with dichloromethane (3 x 200ml) and the DCM extracts are combined and washed sequentially with water (50ml) and saturated brine (50ml), dried ($MgSO_4$), filtered and concentrated to about 50ml volume of DCM under reduced pressure. The resulting suspension is filtered, washed with n-hexane and dried to give the title compound as a colourless solid. The filtrate

and washings were evaporated to give a beige solid which was sonicated in hexane/DCM, filtered, washed with hexane and dried to give further pure 6-(4-Chloro-3-fluoro-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one.

h) Preparation of 6-(4-Chloro-3-cyclopropylmethoxy-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one: To a stirred solution of 6-(4-chloro-3-fluoro-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one (6g, 0.0185mol) and cyclopropylcarbinol (7.35ml, 0.09mol) in dry N-methylpyrollidinone (75ml) is added, portionwise, sodium hydride (60% dispersion on mineral oil, 3.6g, 0.09mol). When addition is complete, the mixture is heated at 60°C for 2h, cooled to room temperature and poured into water (300ml). The mixture is extracted with cyclohexane (2 x 100ml) to remove the mineral oil and then extracted with ethyl acetate (5 x 100ml). The ethyl acetate extracts are combined and washed with water (200ml) and then saturated brine (100ml), dried ($MgSO_4$), filtered and evaporated to give a colourless solid. This is recrystallised from ethyl acetate to give 6-(4-Chloro-3-cyclopropylmethoxy-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one after drying. ^1H NMR ($CDCl_3$, 400MHz) δH (ppm) 11.51 (1H, br s), 8.06 (1H, s), 7.69 (1H, s), 7.41 (1H, d, J = 7.8Hz), 6.87-6.84 (2H, m), 3.91 (2H, d, J = 6.7Hz), 3.14 (1H, m), 2.57 (3H, s), 1.33 (1H, m), 1.22 (6H, d, J = 6.8Hz), 0.67 (2H, m), 0.39 (2H, m); HPLC RT = 6.8minutes (Phenomenex Luna C18 3 micron column (30 x 4.6mm); gradient elution: 10-100% MeCN in water (+0.08% formic acid) over 10 minutes at 3.0mL/minute); MH+ 383.

Example 2: Preparation of 6-(4-Chloro-3-propoxy-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one

a) Preparation of 4-Bromo-1-chloro-2-propoxybenzene: To a stirred solution of n-propanol (10.8ml, 0.143mol) in dry DMF (250ml) at 0°C is added, portion-wise, sodium hydride (60% dispersion on mineral oil, 5.72g, 0.143mol). When addition is complete, the mixture is stirred at 0°C until effervescence had subsided. The mixture of sodium propoxide thus produced is added to a cooled (0°C) solution of 4-bromo-1-chloro-2-fluorobenzene (10g, 0.048mol) in dry DMF (40ml) and then allowed to warm to room temperature over 18h. The volume of DMF is reduced *in vacuo* and the residue poured into water (500ml). The mixture is extracted with diethyl ether (3 x 200ml) and the ether extracts are combined and washed with water (250ml) and then saturated brine (100ml), dried ($MgSO_4$), filtered and evaporated to give a

colourless oil. Purification by column chromatography on silica gel (110g) using cyclohexane as eluant gave 4-Bromo-1-chloro-2-propoxybenzene.

b) Preparation of 4-Chloro-3-propoxybenzeneboronic acid: A stirred solution of 4-bromo-1-chloro-2-isopropoxybenzene (11.98g, 0.048mol) and triisopropylborate (12.26ml, 0.053mol) in dry THF (200ml) under argon is cooled to -78°C and n-butyllithium (21.1ml of a 2.5M solution in hexanes, 0.053mol) is added dropwise. The reaction mixture is allowed to warm gradually to room temperature over 8h before it is quenched by the addition of 2M hydrochloric acid (100ml) and stirred at room temperature overnight. Most of the THF is removed under reduced pressure and the mixture is diluted with diethyl ether (500ml). The ether layer is separated and washed with water (3 x 200ml) and then saturated brine (100ml), dried ($MgSO_4$), filtered and evaporated to give a colourless solid. This is sonicated with n-hexane, filtered and dried to give 4-Chloro-3-propoxybenzeneboronic acid as a 2:1 mixture with the corresponding cycloboroxane. ^1H NMR ($CDCl_3$, 400MHz) δH (ppm) 7.72-7.68 (2H, m), 7.50 (1H, d, J = 7.8Hz), 7.39 (0.5H, d, J = 7.8Hz), 7.31 (0.5H, br d), 7.19 (0.5H, dd, J – 1.2, 7.8Hz), 4.59 (0.77H, br s, $B(O\underline{H})_2$ partially exchanged), 4.14 (2H, t, J = 6.5Hz), 4.04 (1H, t, J = 6.5Hz), 1.97-1.91 (2H, m), 1.90-1.83 (1H, m), 1.13 (3H, t, J = 7.4Hz), 1.08 (1.5H, t, J = 7.4Hz).

c) Preparation of 4-Amino-4'-chloro-6-isopropyl-3'-propoxy-biphenyl-3-carboxylic acid methyl ester: To a stirred mixture of 4-chloro-3-propoxybenzeneboronic acid (4.4g, 0.021mol), 2-amino-5-iodo-4-isopropyl-benzoic acid methyl ester (5.24g, 0.0164mol) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) (0.4g, 0.49mmol) in dry DMF (100ml) under argon is added sodium carbonate (41ml of a 2M aqueous solution, 0.082mol). The mixture is heated at 80°C for 16h, cooled to room temperature and poured into diethyl ether (500ml). The ether layer is separated, washed with water (3 x 200ml) and then saturated brine (50ml), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a brown syrup. Purification by column chromatography on silica gel using cyclohexane and then cyclohexane/ethyl acetate (50:1) as eluant followed by recrystallisation from n-hexane gave 4-Amino-4'-chloro-6-isopropyl-3'-propoxy-biphenyl-3-carboxylic acid methyl ester.

d) Preparation of 6-(4-Chloro-3-propoxy-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one: Hydrogen chloride gas is bubbled through a solution of 4-amino-4'-chloro-6-isopropyl-3'-propoxy-biphenyl-3-carboxylic acid methyl ester (4.9g, 0.0136mol) in dry acetonitrile (100ml)

for 15min at room temperature. The bubbling is then stopped and the mixture heated at reflux for 90min, cooled to room temperature and the volatiles removed under reduced pressure. The colourless residue is partitioned between water (500ml) and ethyl acetate (250ml) and sodium bicarbonate is added portion-wise until no further CO_2 evolution took place. The ethyl acetate phase is separated and washed sequentially with water (200ml) and saturated brine (50ml), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resulting colourless solid is suspended in boiling n-hexane (250ml) and ethyl acetate (250ml) is added until the solid dissolved. Upon cooling, this gave colourless crystalline product (*6*-(4-Chloro-3-propoxy-phenyl)-7-isopropyl-2-methyl-3H-quinazolin-4-one) and further pure material is recovered by evaporating the mother liquor. ^{1}H nmr ($CDCl_3$, 400MHz) δH (ppm) 10.36 (1H, br s), 8.06 (1H, s), 7.68 (1H, s), 7.41 (1H, d, J = 8.0Hz), 6.86 (1H, d, J = 1.8Hz), 6.83 (1H, dd, J = 1.8, 8.0Hz), 4.01 (2H, t, 6.5Hz), 3.15 (1H, m), 2.55 (3H, s), 1.91-1.85 (2H, m), 1.22 (6H, d, J = 6.8Hz), 1.08 (3H, t, J = 7.4Hz); Calc. C 68.01%, H 6.25%, N 7.55%; Found C 67.71%, H 6.00%, N 7.46%; Melting point 236°C; HPLC RT = 7.04minutes (Phenomenex Luna C18 3 micron column (30 x 4.6mm); gradient elution: 10-100% MeCN in water (+0.08% formic acid) over 10 minutes at 3.0mL/minute); MH+ 371.

In the following examples compounds of formula I wherein R^2 is isopropyl and R^3 is methyl are prepared analogously to the Examples above:

Example	R^1	MS	HPLC retention time [min]
3	4-chloro-phenyl	311.2 M-H-	4.93*
4	3,5-dichloro-phenyl	348.7 MH+	5.51*
5	I	329.1 MH+	4.1*
6	2,5-dichloro-phenyl	347.2 MH+	5.34*
7	3-methoxy-4-chloro-phenyl	343 MH+	4.92*
8	3-ethoxycarbonyl-4-methoxy-phenyl	381.4 MH+	4.15*
9	3-furyl	269.1 MH+	4.27*
10	4-chloro-3-ethoxy-phenyl	357 MH+	5.33*
11	3-ethoxy-4-methoxy-phenyl	352 M+	4.3*
12	benzo[1,3]dioxol-5-yl	322 M+	4.3*
13	2,2-difluorobenzo[1,3]dioxol-5-yl	359.5 MH+	5.24*
14	3-chloro-5-methoxy-phenyl	343.3 MH+	5.11*
15	3-chloro-5-ethoxy-phenyl	357.2 MH+	6.9*

16	4-chloro-3-isopropoxy-phenyl	371 MH+	6.7**
17	4-chloro-3-(2-methylpropoxy)-phenyl	385 MH+	7.5**
18	3,5-dichloro-4methoxy-phenyl	377 MH+	6.82*
19	2,5-dimethyl-3-furyl	297 MH+	5.3*
20	3,5-dichloro-4-hydroxy-phenyl	363.1 MH+	5.75*
21	2,4-dichloro-5-ethoxy-phenyl	391.1 MH+	7.1**
22	5-methyl-isoxazol-3-yl	284.1 MH+	4**
23	4-chloro-3-cyclopropylmethoxy-phenyl	383 MH+	6.8**
24	4-chloro-3-fluoro-phenyl	331 MH+	5.7**
25	4-chloro-3-(2-methoxyethoxy)-phenyl	387 MH+	5.6**
26	4-chloro-3-butoxy-phenyl	385 MH+	7.5**
27	4-chloro-3-(tetrahydrofuran-2-ylmethoxy)-phenyl	413 MH+	6.7**
28	4-chloro-3-(3-dimethylaminopropoxy)-phenyl	414 MH+	3.74**
29	4-chloro-3-(2,2-dimethyl)-propoxy-phenyl	399 MH+	8.14**
30	4-chloro-3-propoxy-phenyl	371.2 MH+	7.05**
31	4-chloro-3-(tetrahydrofuran-3-ylmethoxy)-phenyl	413 MH+	6.1**
32	4-chloro-3-(2-dimethylaminoethoxy)-phenyl	397.3 M+	3.33**
33	4-chloro-3-(3-methylbutoxy)- phenyl	398.3 M+	7.96**
34	4-chloro-3-cyclopentoxy-phenyl	397.2 MH+	7.56**
35	3-bromo-5-methyl-phenyl	371 MH+	6.77**
36	4-chloro-3-(1-methylpyrrolidin-3-yloxy)-phenyl	412.4 MH+	3.66**
37	4-chloro-3-(fur-3-ylmethoxy)-phenyl	409.2 MH+	6.68**
38	4-chloro-3-(2-methyl-cyclopropylmethoxy)-phenyl	397.2 MH+	7.38**
39	4-chloro-3-(2-isopropoxyethoxy)-phenyl	414.4 M+	6.75**
40	4-chloro-3-(2-ethoxyethoxy)- phenyl	400.4 M+	6.34**
41	3-chloro-4-methyl-phenyl	327.2 MH+	6.44**
42	4-chloro-3-(2-phenethyloxy)-phenyl	433.2 MH+	7.62**

43	4-chloro-3-[2-(2-methoxyphenyl)ethoxy]-phenyl	463.3 MH+	7.72**
44	4-chloro-3-(2-cyclopropylethoxy)-phenyl	397.2 MH+	7.53**
45	4-chloro-3-(1-methyl-cyclopropyl-methoxy)-phenyl	399.3 M+	7.48**
46	4-chloro-3-cyclobutylmethoxy-phenyl	397.2 MH+	7.72**
47	4-chloro-3-propylsulfanyl-phenyl	387.2 MH+	7.36**
48	4-chloro-3-[2-(4-methoxy-phenyl)-ethoxy]-phenyl	463.3 MH+	7.49**
49	4-chloro-3-(1,1dimethyl-propoxy)-phenyl	398.5 M+	7.53**
50	4-chloro-3-(3-fluoro-propoxy)-phenyl	389 MH+	6.54**
51	4-chloro-3-[2-(3-methoxy-phenyl)-ethoxy]-phenyl	463.3 MH+	7.49**
52	4-chloro-3-(3-methylsulfanyl-propoxy)-phenyl	417.2 MH+	7.09**
53	4-chloro-3-methyl-phenyl	327.2 MH+	6.49**
54	4-chloro-3-[2-(2-methoxy-ethoxy)ethoxy]-phenyl	431.3 MH+	5.82**
55	4-chloro-3-[((Z)-propenyl)oxy]-phenyl	369 MH+	6.97**
56	4-chloro-3-(2-propoxy-ethyl)-phenyl	399 MH+	7.17**
57	4-chloro-3-allyloxy-phenyl	369 MH+	6.62**
58	4-chloro-3-(3-methoxy-butoxy)-phenyl	415.2 MH+	6.65**

Example 59: Preparation of 2-Amino-6-(4-chlorophenyl)-7-isopropyl-3H-quinazolin-4-one.

a) Preparation of 4-Amino-4'-chloro-6-isopropylbiphenyl-3-carboxylic acid: A suspension of 4-amino-4'-chloro-6-isopropylbiphenyl-3-carboxylic acid methyl ester [prepared analogously to examples above] (0.95 g, 3.13 mmol) in methanol (20 mL) under a nitrogen atmosphere was treated with 5M KOH solution (12 mL), and the mixture is heated at 80 ºC for 1 h. Upon cooling to room temperature, the mixture is partitioned between ethyl acetate (50 mL) and water (100 mL) and extracted. The aqueous phase is washed with fresh ethyl acetate (50 mL). The aqueous phase is acidified to pH3 with conc. HCl solution, and extracted with ethyl acetate (2 x 50 mL). The combined organic layers are dried (anhydrous $MgSO_4$), filtered and the solvent is removed under reduced pressure to afford the crude title compound as a

brown semi-solid residue. This is used without further purification, although a small sample is purified by flash chromatography (1:1 ethyl acetate-hexanes) for analytical purposes.

b) Preparation of 6-(4-Chlorophenyl)-7-isopropyl-1H-benzo[d][1,3]oxazine-2,4-dione: A stirred suspension of 4-amino-4'-chloro-6-isopropylbiphenyl-3-carboxylic acid (0.8 g, 2.76 mmol) in anhydrous dioxane (15 mL) is treated at room temperature with trichloromethyl chloroformate (2.18 g, 11.04 mmol). The mixture is heated under reflux for 6 h. Upon cooling to room temperature, methanol (3 mL) is added and the mixture is concentrated by evaporation under reduced pressure. The resulting brown solid is recrystallized from absolute ethanol to afford the title compound as off-white crystals.

c) Preparation of 2-Amino-6-(4-chlorophenyl)-7-isopropyl-3H-quinazolin-4-one: A stirred suspension of 6-(4-chlorophenyl)-7-isopropyl-1H-benzo[d][1,3]oxazine-2,4-dione (0.216 g, 0.68 mmol), 2-ethyl-2-thiopseudourea hydrobromide (0.126 g, 0.68 mmol) and Na_2CO_3 (0.145 g, 1.37 mmol) in MeCN (10 mL) is heated under reflux for 35 min. The condenser is removed and the bulk of the solvent is driven off. *m*-Xylene (6 mL) is added, the condenser is replaced and the temperature of the oil bath is raised to 150 ºC. A small pellet of NaOH is added, and the mixture is heated under reflux for 2.5 h. Upon cooling to room temperature, the mixture is partitioned between 0.5M NaOH solution (150 mL) and ethyl acetate (50 mL) and extracted. The aqueous phase is extracted with fresh ethyl acetate (50 mL). The combined organic layers are backwashed with brine (100 mL) and dried (anhydrous $MgSO_4$). The solvent is removed under reduced pressure to afford the crude title compound as an off-white solid. This is recrystallized from absolute ethanol to afford pure compound. Mp 326-330 ºC. ^{1}H nmr (DMSO-d_6, 400MHz) δH (ppm) 10.89 (1H, s, exchanges with D_2O), 7.58 (1H, s), 7.5-7.47 (2H, dd, J = 1.8, 8.4 Hz), 7.33-7.31 (2H, dd, J = 1.8, 6.5 Hz), 7.18 (1H, s), 6.31 (2H, br s, exchanges with D_2O), 2.98-2.94 (1H, m), 1.13-1.12 (6H, d, J = 6.8 Hz). HPLC RT = 4.4minutes (Phenomenex Luna C18 3 micron column (30 x 4.6mm); gradient elution: 10-100% MeCN in water (+0.08% formic acid) over 10 minutes at 3.0mL/minute); MH+ 314.06 (100%).

In the following examples compounds of formula I wherein R^2 is isopropyl and R^3 is NH_2 are prepared analogously to the above Example 59:

60	4-chloro-3-cyclopropylmethoxy-phenyl	384.2 MH+	5.08**

In the following examples compounds of formula I wherein R^2 is isopropyl and R^3 is methyl are prepared analogously to Examples 1 or 2:

Example	R^1	MS	HPLC retention time [min]
61	4-chloro-3-(2-ethoxy-ethyl)-phenyl	385.3 MH+	4.98**
62	4-chloro-3-ethoxymethyl-phenyl	371.3 MH+	4.92**
63	4-chloro-3-(tetrahydro-furan-3-yloxy)-phenyl	399.3 MH+	5.83**
64	4-chloro-3-(2-hydroxy-ethoxy)-phenyl	373.3 MH+	4.95**
65	4-methoxy-3-propoxy-phenyl	367.4 MH+	5.69**
66	3-amino-4-chloro-phenyl	328.2 MH+	5.23**
67	3-butylamino-4-chloro-phenyl	384.3 MH+	7.33**
68	3,4-difluoro-5-propoxy-phenyl	373.3 MH+	6.80**
69	3,4-difluoro-5-methoxy-phenyl	345.3 MH+	4.36**
70	3-(2-chloro-ethoxy)-4,5-difluoro-phenyl	393.2 MH+	6.42**
71	3,4-difluoro-5-(3-methoxy-butoxy)-phenyl	417.3 MH+	6.58**

HPLC conditions:

* Phenomenex Kingsorb 3 micron C18 column (30x4.6mm), gradient elution 10-100% MeCN in water (+0.1%TFA) over 10 minutes at 3.0mL/min.

** Phenomenex Luna reverse phase C18 3 micron 30 x 4.6mm; Gradient elution 10% MeCN in water (+0.08% formic acid) to 100% MeCN over 10 min (rate = 3.0 mL/min).

Example 72: Soft Capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in the preceding Examples, are prepared as follows:

Composition

Active ingredient	250 g
Lauroglycol	2 litres

Preparation process: The pulverized active ingredient is suspended in Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer to produce a particle size of about 1 to 3 μm. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.